Subject Selection and Recruitment

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- *The views expressed are mine and do not necessarily represent the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services*

Subject selection and recruitment

- Successful clinical research *depends* on:
  - Recruiting the right number and type of research subjects
  - In a reasonable time frame

- *Common challenge*: how to successfully find and recruit subjects

Ethics of Subject Selection

- Maintain value and validity
- Minimize risks and maximize benefits
- Fairly distribute research burdens and benefits
- Demonstrate respect for individuals and communities

Selection of subjects

- The primary criteria is scientific
- Who (number and characteristics) will best answer the scientific question(s)?

Belmont Report

- "…selection of subjects needs to be scrutinized…to determine whether some classes (e.g. welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied"

Further considerations

- Are some scientifically appropriate individuals or groups particularly…
  - susceptible to risk or burden?
  - likely to benefit from the research?
  - vulnerable?

Research as a risk--protection

- Protection from bearing the burdens or risks of research
- Exclusion of some already burdened groups or individuals
- Additional protections for those who are vulnerable

Research as a benefit--access

- Access to the benefits of research participation.
- Access to benefit from the application of study results
- Exclusion seen as unfair, discriminatory.

Balance between protectionism and access

Who should be selected?

- Exclusion without a good reason may be unfair or discriminatory.

- “People are clamoring for access to clinical trials...demanding they, and others like them, are owed such as a matter of justice” (Levine, 1994)

Priority of Science

- The scientific goals of the study should be the *primary* consideration in determining who can enroll.
- This involves ensuring the value of the study and enhancing its validity.

Exclusion for scientific reasons

- For example, those inappropriate to the question

- Those who cannot satisfy the study requirements

Minimize Physical Risks

- Exclude individuals who would face significantly higher risks.
- For instance, individuals with poor kidney function in a phase II study of a drug with renal clearance.

Maximize Benefits

- Select subjects who are more likely to benefit from participation.
- For instance, a study of a new anti-HIV drug may focus on individuals with low CD4 counts.

Exclusion for vulnerability

- The vulnerable who are not necessary to answer the question
- The vulnerable when not adequately protected by safeguards

Protecting the Vulnerable

- There is an order of preference in selecting subjects, for instance, adults before children. (Belmont Report)
- Exclude vulnerable subjects unless their participation is needed for scientific reasons. (CIOMS 2002)

Address Vulnerability First

- In some cases, it is possible to address individuals' vulnerability without having to exclude them.

- For instance, individuals who do not understand English may be vulnerable, but this vulnerability can be addressed by provision of translators and translated documents.

Who is “Vulnerable” ??

- Children
- Prisoners
- Pregnant women
- Mentally disabled persons
- Economically or educationally disadvantaged persons
- Institutionalized persons
- Very sick or terminally ill patients
- Dependent persons
- Etc.

Subject Selection: vulnerability

- People are vulnerable when they cannot protect their own interests through informed and voluntary consent

- Should they be excluded or can adequate additional protections be put in place?

How might people be vulnerable?

- Reduced capacity to communicate or understand
- Reduced capacity to deliberate and make a decision
- Real or perceived expectations of reward, retribution, or ‘deference’

Safeguards

- Exclude
- Promote autonomous decision making
- Proxy consent
- Process modifications

Subjects unable to consent

- Proxy consent may be acceptable for enrolling those who cannot consent for themselves

Selecting a Community

- In some cases, investigators have a choice of possible communities to do research.

- The principles of subject recruitment apply in deciding which community to select.

Subject Selection

- Taking all of the above considerations into account, eligibility and exclusion criteria are delineated

- Recruitment begins

Recruitment

- *Find* subjects
- *Inform* them of the nature, risks, benefits, and alternatives, etc.
- Provide *incentives* to participate
- *Invite* them to participate
- *Enroll* them.

Methods of finding subjects

- Targeted recruitment
- Referrals from professional colleagues
- Advertisement
- Advocacy groups
- Databases
- Own patients

Advertising

- How much effect does advertising have on recruitment?
- Does advertising affect consent?
- May benefits be advertised?
- Must risks be advertised?

IRBs and Advertising

- "The IRB should review the methods and material that investigators propose to use to recruit subjects."
- Ads should not claim that investigational interventions are safe or effective.
- IRB should evaluate the "relative size of type used and other visual effects."

www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting

Ads in Real Life: Bar Coaster

Research Subjects Wanted

Earn $50-$1295

Call
555-555-5555

Christine's Research Institute

Why do people participate in research?

- Hope for therapeutic benefit
- Trust in physician
- Altruism, contribution to science or society
- Medical care otherwise unattainable
- Money
- Academic or other ‘rewards’
- Other

Incentive

- Something that incites to action, or moves someone to do something

- Synonyms: stimulus, motive, spur, incitement, encouragement

Incentives to participate

- May provide or add a reason for some people to participate
- In some cases, enable participation

Incentives in clinical research

- Free care and treatment
- Access to services (health and other)
- Money
- Gifts
- Promotions, references
- Etc.

Offering money as an incentive

Concerns about offering money to research participants

- Coercion
- “Undue inducement”
- Preferential enrollment of poorer populations

Coercion

- Coercion is a threat of physical, psychological, or social harm in order to compel someone to do something, such as participate in research.
  - e.g. threat of punishment (e.g. by the police, court, military officer, professor, employer)
  - threat of physical or other harm (e.g. death, injury, loss of a job or a promotion)

Coercion

- Money is an offer or an opportunity, and not a threat of harm. Person is not made worse off if chooses not to participate
- Coercion is a serious allegation, should not be used lightly
- An offer of money is not coercion

Undue influence (inducement)

- “An offer one cannot refuse”
- “Controlling and irresistible, yet unwelcome”
- Strong enough to compel someone to participate against their better judgment

Why worry about undue influence in research?

- An inducement is undue if it is "…so attractive [that it] can blind prospective subjects to potential risks or impair their ability to exercise proper judgment"

- [or] "prompt them to lie or conceal information that would disqualify them from enrolling--or continuing--in research"

Official IRB Guidebook OHRP

Do financial incentives blind prospective subjects to research risks?

- What are the risks and would subjects be asked to accept them without financial incentives?
- Limited data suggest payment does not obscure risk perception (e.g. Halpern et al. Archives 2004)
- Can evaluate understanding of risks

Do financial incentives impair judgment?

- Voluntary decisions are motivated by various factors, often including but not limited to money.
- Money is a factor in many decisions.
- Money is one factor in the research decisions of some participants

- Most participants (75%) in one study thought $500 could impair the judgment of others, but fewer (20%) that it would impair their own judgment.

    - Casarett et al. *J Gen Intern. Med*. 2002

Should we worry about undue Inducement?

- If an offer is so attractive that people exercise *poor judgment* about research participation that involves a *risk of serious harm*, but
- IRBs do not approve studies that expose subjects to serious risk of harm,
- Payment cannot be undue inducement in an appropriately approved study

Emanuel, *J Law Med Ethics*. 2004.

Undue inducement

- “I’ll know it when I see it”
- Decisions left to investigators and IRBs
- Caution at the ends of the risk spectrum or in settings where subjects might have values that conflict with the research.

- Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement").
  - CIOMS International Ethical Guidelines

Money for research participation

- Money may also
  - Minimize financial sacrifice
  - Provide compensation for time and effort
  - Be offered as gratitude or reward for contribution